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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/025,222	PELLETIER ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-72 and 84-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *88* is/are allowed.

6)☒ Claim(s) *66-72,84-87 and 89-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/31/03; 04/05/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 66-72 and 84-91 are pending in the application.

[2] Applicants' amendment to the claims, filed April 05, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicants' amendment to the specification, filed April 05, 2004, is acknowledged.

[4] Receipt of an information disclosure statement (IDS), filed April 05, 2004, is acknowledged. All cited references have been considered by the examiner and a copy of the IDS is attached to the instant Office action.

[5] Applicants' arguments filed on April 05, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35, U.S. Code not included in the instant action can be found in a prior Office action.

Specification/Informalities

[7] In view of applicants' amendment to the specification, the objections to the specification as set forth in items [4] and [5] of the Office action mailed January 05, 2004 are withdrawn.

Claim Objections

[8] In view of applicants' amendment to the specification, the objections to the claims as set forth in items [6] and [7] of the Office action mailed January 05, 2004 are withdrawn.

[9] In view of the amendment filed April 05, 2004, claim(s) 91 is objected to because of the following informalities: the term "said primase possess a biological activity" is grammatically incorrect and should be replaced with, for example, "said primase possesses a biological activity". Appropriate correction is required.

Claim Rejections - 35 USC § 101

[10] In view of applicants' amendment to the claims, the rejections of claims 66-72 and 81-91 under 35 U.S.C. 101 as set forth in items [8] and [9] of the Office action mailed January 05, 2004 are withdrawn.

Claim Rejections - 35 USC § 112, Second Paragraph

[11] In view of applicants' amendment to the claims, the rejection of claims 66-71 and 84-91 under 35 U.S.C. 112, second paragraph, as set forth in items [10]-[12] of the Office action mailed January 05, 2004 is withdrawn.

Claim Rejections - 35 USC § 112, First Paragraph

[12] Claims 66-71, 84-85, and 91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Claims 66 (claims 67-69 dependent therefrom) and 70 (claim 71 dependent therefrom) recite the limitation of a polypeptide comprising "less than 566 amino acids of SEQ ID NO:2." Applicants assert that support for this amendment can be found "in Figure 10 and page 105 of the specification" as "a polypeptide fragment of 565 amino acids was produced, and shown to have bacteriophage polypeptide binding activity" (page 7, top of the instant response). Although not expressly stated by applicants, it would appear that this 565 amino acid fragment is amino acids 35-599 of SEQ ID NO:2. However, it is noted that the recited fragment is not limited to amino acids 35-599 of SEQ ID NO:2 or a polypeptide comprising amino acids 35-599 of SEQ ID NO:2. Also, claims 84-85 and 91 recite the limitation of a polypeptide comprising "amino acids 1 to 34 of SEQ ID NO:2" or variants thereof. No remarks have been provided as to where support for this limitation can be found in the specification, claims, or drawings as originally filed. The examiner can find no support for the limitation of a polypeptide comprising "less than 566 amino acids of SEQ ID NO:2" or a polypeptide comprising "amino acids 1 to 34 of SEQ ID NO:2" or variants thereof in the specification, claims, and drawings as originally filed. In the even the examiner has inadvertently overlooked

such support, the examiner requests that applicants direct the examiner to support for these limitations.

[13] The written description rejection of claims 66-72, 84-87, and 89-91 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item [13] of the Office action mailed January 05, 2004 and for the reasons stated below.

In summary, the examiner rejected the claims because the specification fails to describe a representative number of species of the genus of claimed polypeptides, which encompasses widely variant species with respect to structure and/or function.

Applicants argue that the specification describes thirteen different fragments (shown in Figure 10) of SEQ ID NO:2, seven of which have bacteriophage polypeptide binding activity. Applicants argue these representative species are sufficient to describe the claimed genus of polypeptides according to MPEP 2163 and *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Applicants' argument is not found persuasive.

Applicants' arguments are not commensurate in scope with the claims. The claimed polypeptide is not limited to those fragments shown in Figure 10. Instead, the claims encompass a vast number of widely variant species with respect to both structure and function, comprising a fragment or variant of SEQ ID NO:2 having any activity, including non-functional polypeptides (claims 84-87 and 89-91), having the activity of binding to any bacteriophage polypeptide (claims 66-67 and 70-72), and/or having an activity selected from the range of biological activities including DNA polymerase activity, RNA primase activity, stimulation of helicase activity of S. aureus DnaC helicase, or stimulation of ATPase activity of S. aureus DnaC helicase. In this

case, neither full length SEQ ID NO:2 or the fragments thereof as shown in Figure 10 are sufficient to represent the entire genus of claimed polypeptides.

Applicants argue the species encompassed by the genus of claimed polypeptides share a structural feature as a minimal domain of the 39 amino acids at the carboxy terminus is required for bacteriophage binding activity. Applicants further argue that each member of the genus has the same functional feature of bacteriophage binding activity. Applicants' argument is not found persuasive.

Regarding the asserted structural feature shared by all members of the genus, it is noted that applicants' arguments are not commensurate in scope with the claims. While not expressly stated by applicants, it appears that applicants are referring to the 39 carboxy terminal amino acids of SEQ ID NO:2 in their argument. There is no dispute that the evidence presented in Figure 10 would suggest that a portion of the C-terminus of SEQ ID NO:2 is required for interaction with bacteriophage polypeptide 96ORF78. However, there is no way to know from Figure 10 as to whether the 39 carboxy terminal amino acids of SEQ ID NO:2 is the "minimal domain" required for interaction with bacteriophage polypeptide 96ORF78. For example, it is possible that a subsequence of the 39 carboxy terminal amino acids of SEQ ID NO:2 is the "minimal domain" for interaction with bacteriophage polypeptide 96ORF78. Regardless, it is noted that there is no limitation in the claims that requires that the 39 carboxy terminal amino acids of SEQ ID NO:2 be present in all members of the claimed genus of polypeptides. Even assuming arguendo this structural feature was possessed by all members of the claimed genus, it is noted that this feature does not constitute a "substantial portion"

(underline added for emphasis) of the genus that is commonly shared by all members. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Further, it should be noted that none of the claims requires interaction with bacteriophage polypeptide 96ORF78, and instead encompass species that are not limited to binding a bacteriophage polypeptide (claims 84-91), encompass species that bind any bacteriophage polypeptide (claims 66-67 and 70-72), encompass species that bind any bacteriophage 96 polypeptide (claim 68), or encompass species that bind any polypeptide variant of 96ORF078 (claim 69).

Regarding the asserted functional feature shared by all members of the genus, applicants' arguments are not commensurate in scope with the claims. It should be noted that none of the claims recites an activity of "bacteriophage binding activity" as argued by applicants. It appears that applicants intended activity is bacteriophage polypeptide binding activity, which is recited in e.g., claim 1. Even if applicants' intended activity is bacteriophage polypeptide binding activity, there is no limitation in claims 84-91 that requires all members of the genus to have bacteriophage polypeptide binding activity. Even for those claims that are limited to the function of bacteriophage polypeptide binding, the genus encompasses widely variant species with respect to function as the members of the genus have the ability to bind any bacteriophage polypeptide or any bacteriophage 96 polypeptide and any other biological activity. Moreover, the specification fails to identify a known or disclosed correlation between the function of binding any bacteriophage polypeptide and structure of a polypeptide required for such activity.

Applicants argue that in view of the disclosure, a skilled artisan could make and use variants of SEQ ID NO:2 with very minor sequence modifications that maintain the ability to bind phage polypeptides without undue experimentation. Applicants argue that given the knowledge of the 39 amino acid minimal domain and the art-recognized procedure for preparing variants, the skilled artisan could predict whether a particular fragment would fall within the scope of the claims and could identify additional DnaG fragments or variants that bind to 96ORF78. Applicants' argument is not found persuasive.

Applicants' arguments appear to address the scope of enablement rejection and not the instant written description rejection. However, to the extent MPEP 707.07(f) requires the examiner to answer all material traversed, applicants' arguments are addressed below. While applicants do not specify a number or type of modification(s) that is/are considered to be "very minor", it is the examiners position that the claims are not drawn to polypeptides having "very minor sequence modifications" to SEQ ID NO:2. The most limited claim with respect to variation is claim 86, which is drawn to a polypeptide that is at least 95% identical to SEQ ID NO:2. The paper copy of the sequence listing indicates that SEQ ID NO:2 is 599 amino acids in length. As such, up to 5% of the 599 amino acids of SEQ ID NO:2 can be altered in any way, e.g., amino acid addition, substitution, deletion, and insertion, such that the sequence maintains the identity limitation. Even if the claims were limited to polypeptides having "very minor sequence modifications" to SEQ ID NO:2, it is noted that the claims do not require that all members of the genus have the "39 amino acid minimal domain" and it is further

noted that claims 84-91 are not limited to those variants "that bind to the bacteriophage polypeptide 96ORF78."

There is no dispute that methods of modifying a polypeptide sequence are well known in the art. However, the effects of modifying a polypeptide sequence are highly unpredictable (as evidenced by Branden et al. "Introduction to Protein Structure", Garland Publishing Inc., New York, 1991; cited in the Office action mailed January 05, 2004). In this case, the specification fails to identify even a single variant of SEQ ID NO:2 that maintains the recited function. As stated in a previous Office action, while MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". As the effects of altering an amino acid sequence with an expectation of maintaining the ability to bind to a bacteriophage polypeptide are highly unpredictable, the single disclosed representative species of SEQ ID NO:2 fails to represent the entire genus of claimed polypeptides.

[14] The scope of enablement rejection of claims 66-72, 84-87, and 89-91 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item [14] of the Office action mailed January 05, 2004 and for the reasons stated below.

In summary, the claims are rejected because the specification, while being enabling for the isolated polypeptide of SEQ ID NO:2, does not reasonably provide enablement for the full scope of claimed polypeptides.

Applicants argue that the specification provides a representative number of species of the claimed genus of polypeptides, which is allegedly well-defined in both structure and function. Applicants argue that given the knowledge of the skilled artisan and the teachings of the disclosure, a skilled artisan would be able to make and use the full scope of the claimed invention without undue experimentation. Applicants' argument is not found persuasive.

Applicants' argument (in part) addresses the written description rejection and not the instant scope of enablement rejection. However, to the extent MPEP 707.07(f) requires the examiner to answer all material traversed, applicants' arguments are addressed below. For those reasons addressing the written description rejection, it is the examiner's position that the specification fails to describe the genus of claimed polypeptides. Furthermore, it is the examiner's position that even in view of the disclosure of the specification, a skilled artisan would not be able to make and/or use the full scope of claimed polypeptides as discussed in detail below.

Addressing the breadth of the claims, applicants assert the claims are not overly broad, arguing that: 1) claims 66-71 are limited to polypeptides having less than 566 amino acids that bind a bacteriophage polypeptide, which are limited to polypeptides that are defined by structure and activity; 2) the polypeptide of claim 72 is limited to having domains of a specific origin, i.e., derived from SEQ ID NO:2 or derived from a bacteriophage polypeptide, that must also possess a specific physical property of binding to each other; 3) the polypeptides of claims 84-91 have a very high level of identity or similarity with a reference polypeptide; 4) the specification describes at least

thirteen DnaG polypeptide fragments; 5) a specification may contain a written description of a broadly claimed invention without describing all species encompassed by the claim (citing Utter V. Hiraga); and 6) in the case of Amgen Inc. v Hoechst Marion Roussel Inc., the court found that a skilled artisan could, without undue experimentation, resolve gaps between the disclosure and the claim breadth. Applicants' argument is not found persuasive.

Addressing arguments 1)-3), it is noted that even after amendment, the claims are not commensurate with the enablement provided by the specification. Claims 66-71 are so broad as to encompass all polypeptides comprising any fragment or variant of less than 566 amino acids of SEQ ID NO:2 and binds to any bacteriophage polypeptide, optionally having a biological activity selected from those recited in claim 67, optionally wherein the bacteriophage polypeptide is limited to any bacteriophage 96 polypeptide and optionally wherein the bacteriophage 96 polypeptide is limited to any fragment or variant of 96ORF078, and optionally wherein the fragment is selected from those recited in claim 71. Similarly, even after amendment, claim 72 is so broad as to encompass a composition comprising first and second polypeptide domains that bind to each other, wherein the first domain is any amino acid sequence that is "derived from" SEQ ID NO:2 and wherein the second domain is any amino acid sequence that is "derived from" any bacteriophage polypeptide that binds SEQ ID NO:2. Also, claims 84-91 are so broad as to encompass any polypeptide comprising amino acids 1-34 of SEQ ID NO:2 or variants thereof at least 92% identical to amino acids 1-34 of SEQ ID NO:2 having any function; variants that are at least 95% similar or identical to SEQ ID NO:2 having any function or

optionally having primase activity; any polypeptide comprising an amino acid sequence that is at least 95% or 97% identical to amino acids 1-50 of SEQ ID NO:2 having any function; or any of the polypeptides encompassed by claims 84-91 as listed above having primase activity. Addressing argument 4), it is noted that the claims are not so limited to those thirteen fragments as shown in Figure 10 and instead broadly encompass the polypeptides as described above. Addressing argument 5), it is noted that the holding of the court in Utter was directed to written description and not scope of enablement and neither the instant written description rejection nor the instant scope of enablement rejection is inconsistent with the findings in Utter. Addressing argument 6), the court in Amgen found that, in view of the state of the art, it would not constitute undue experimentation for a skilled artisan to use other mammalian host cells for the expression of human EPO DNA. In contrast to Amgen, undue experimentation would be required to make and use the broad scope of claimed polypeptides, particularly in view of the lack of guidance and working examples, the high level of unpredictability as evidenced by the prior art, and the significant quantity of experimentation required to make and use all claimed polypeptides.

Regarding the presence or absence of working examples, applicants argue: 1) the specification discloses at least thirteen working examples of the claimed invention, which is more than a single working example; 2) non-functional polypeptides or polypeptides having activity other than the activity of SEQ ID NO:2 are either not encompassed by the claims or are explicitly mentioned to be useful for screening, as antigens for diagnostic and therapeutic purposes, and as research agents; and 3) the

prior art discloses mutants of DnaG primase. Applicants' argument is not found persuasive.

Addressing argument 1), it is noted that applicants' argument regarding the thirteen fragments of SEQ ID NO:2 is not commensurate in scope with the claims as the claims are not limited to such fragments and instead encompass polypeptides comprising fragments. Addressing argument 2), it is noted that the vast majority of variants of SEQ ID NO:2 will not be so useful for screening, as antigens for diagnostic and therapeutic purposes, and as research agents. It is well known in the art that an antibody binds a specific antigen in a protein sequence. Modification of this antigen and even sequence outside of the antigen can abolish antibody binding as evidenced by Colman et al. (*Res Immun* 145:33-36) and Abaza et al. (*J Protein Chem* 11:433-444). Similarly, while compounds that bind to and/or inhibit the activity of a variant of SEQ ID NO:2 will not necessarily bind to and/or inhibit SEQ ID NO:2 itself. Moreover, it is noted that the specification fails to provide guidance as to how one is to use antibodies or compounds that bind to variants of SEQ ID NO:2 that are non-functional or have activity other than the activity of SEQ ID NO:2. Regarding argument 3), it is noted that none of applicants' cited prior art references provide guidance or a working example of a variant of SEQ ID NO:2 that would provide a skilled artisan with an expectation of altering the polypeptide of SEQ ID NO:2 with an expectation of success for obtaining a polypeptide having the desired activity.

Regarding the predictability or unpredictability of the art, applicants argue: 1) regarding claims 66-72, knowing the 39 amino acid "minimal domain" for binding

96ORF78, one could identify additional DnaG fragments or variants with the desired activity of binding to a bacteriophage polypeptide; 2) regarding claims 84-91, the claimed polypeptides need not have biological activity to be useful in the production of antibodies and/or use in diagnostic methods; and 3) claims are not invalid if they encompass some inoperative embodiments, citing Atlas Powder Co. v E. I. DuPont de Nemours and Co., 750 F2d 1569, 224 USPQ 409 (Fed. Cir. 1984) and that one could refer to cited prior art references for guidance. Applicants' argument is not found persuasive.

Addressing argument 1), it is again noted that applicants' arguments are not commensurate in scope with the claims as the polypeptides of claims 66-71 are not limited to the 39 amino acid "minimal domain" or to polypeptides comprising this minimal domain. Furthermore, it is noted that none of claims 66-72 is limited to those polypeptides that have the ability to bind 96ORF078. Addressing argument 2), as noted above, It is well known in the art that antibodies and therapeutic compounds bind to specific amino acid sequences. Modification of this amino acid sequence can abolish antibody binding (as evidenced by Colman et al. (*Res Immun* 145:33-36) and Abaza et al. (*J Protein Chem* 11:433-444)) and can similarly abolish compound binding. Moreover, it is noted that the specification fails to provide guidance as to how one is to use antibodies or compounds that bind to variants of SEQ ID NO:2 that are non-functional or have activity other than the activity of SEQ ID NO:2. Addressing argument 3), while it is acknowledged that inoperative embodiments encompassed by a claim do not necessarily render the claimed subject matter non-enabled, MPEP 2164.08(b)

states that "the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable." In this case, the specification fails to provide any guidance as to which amino acids of SEQ ID NO:2 may be altered with an expectation of obtaining a polypeptide having the desired activity. In view of the lack of guidance, the high level of unpredictability, and the significant amount of screening associated with altering an amino acid sequence to obtain a polypeptide having a desired activity, undue experimentation is required to make and/or use all polypeptides encompassed by the claims and consequently, the specification fails to enable the full scope of claimed polypeptides.

Regarding the stated of the prior art and relative skill of those in the art, applicants argue: 1) the examiner's cited prior art is not relevant as Branden et al. refers to "enzymes" and de novo design of proteins and Witkowski et al. concerns alteration of a complex enzyme and the unpredictability for a complex enzyme is much higher than for S. aureus DnaG primase and 2) the state of the art supports a high level of predictability for bacterial DnaG primase activity citing the references as set forth at pages 17-18 of the instant response. Applicants' argument is not found persuasive.

Addressing argument 1), applicants arguments addressing the reference of Branden et al. are found to be confusing as based on the teachings of the specification and applicants' cited prior art references, SEQ ID NO:2 appears to be an enzyme, exhibiting enzymatic activity. Therefore, Branden et al. is relevant to the unpredictability of altering the claimed amino acid sequence as Branden et al. relates to the unpredictability of altering the sequence of an enzyme. If SEQ ID NO:2 does not have

enzymatic activity, applicants are requested to elaborate on the intended activity of the polypeptide of SEQ ID NO:2. With respect to those claimed variants that are not limited to those having the activity of SEQ ID NO:2, the specification fails to provide for using those variants, and as such, fails to enable those claimed polypeptides. With respect to the reference of Witkowski et al., while this reference may relate to another enzyme, the reference is provided to corroborate the teachings of Branden et al., i.e., that even a single amino acid alteration to a protein's sequence can have unexpected effects, which are undisputed by applicants. Addressing argument 2), it is noted that the prior art references provide no guidance for altering SEQ ID NO:2 with an expectation of maintaining the activities of SEQ ID NO:2. In this case, the specification and prior art fail to provide guidance regarding those amino acids of SEQ ID NO:2 that may be altered with an expectation of maintaining the activities of SEQ ID NO:2.

Regarding the amount of direction or guidance and the quantity of experimentation, applicants argue: 1) the specification provides guidance and working examples for fragments and variants; 2) there is not a high level of unpredictability as allegedly evidenced by the cited references; and 3) while further experimentation may be necessary to make and use the full scope of claimed polypeptides, such experimentation is not undue in view of the teachings of the specification.

Addressing arguments 1)-2), for the reasons stated above, the specification and prior art fail to enable the full scope of claimed polypeptides. Addressing argument 3) it is noted that it is not routine to make and test all polypeptides encompassed by the claims for those that have the activities of SEQ ID NO:2. In this case, the specification

merely provides a starting point from which a skilled artisan can make and test the vast number of polypeptides encompassed by the claims for those that have the desired activity. Such guidance amounts to no more than a starting point for further research.

Claim Rejections - 35 USC § 102

[15] The rejection of claim(s) 66-71, 87, and 91 under 35 U.S.C. 102(b) as being anticipated by O'Donnell et al. (WO 99/37661; cited in the IDS filed July 07, 2003 as reference A7), is maintained for the reasons of record as set forth in item [15] of the Office action mailed January 05, 2004 and for the reasons stated below.

In summary, the claims are rejected as O'Donnell et al. teach a polypeptide encoded by *S. aureus dnaG* having primase activity that is 93.5 % identical to SEQ ID NO:2 and is 98.1 % similar to SEQ ID NO:2 (see Appendix A), which anticipates claims 66-71, 87, and 91 as written.

Applicants argue: 1) the polypeptide of O'Donnell et al. comprises 572 amino acids and does not disclose examples of fragments of the polypeptide having less than 572 amino acids; 2) O'Donnell et al. do not teach that their polypeptide can bind to a bacteriophage polypeptide or which domain or how many amino acids of the polypeptide described therein is required for binding a bacteriophage polypeptide; and 3) the polypeptide of O'Donnell et al. has only 92% similarity over the entire length of SEQ ID NO:2. Applicants' argument is not found persuasive.

Nowhere is there a recited limitation in claims 66-71, 87, and 91 that limits the claimed polypeptide to being less than 566 amino acids. Instead, the claimed

polypeptide is limited to comprising "less than 566 amino acids of SEQ ID NO:2." In this regard, it is noted that the polypeptide of O'Donnell et al. has only 560 amino acid matches with SEQ ID NO:2, and thus comprises "less than 566 amino acids of SEQ ID NO:2." In this case, the polypeptide of O'Donnell is a variant of SEQ ID NO:2 that explicitly or implicitly meets all limitations of the claimed polypeptides. It is noted that, as the polypeptide of O'Donnell has the 39 amino acid "minimal binding domain" required to bind to 96ORF78, without evidence to the contrary, the polypeptide of O'Donnell et al. would inherently bind 96ORF78.

[16] In view of applicants' amendment to claims 84 and 89, the rejection under 35 U.S.C. 102(e) as being anticipated by Doucette-Stamm et al. (US Patent 6,380,370) as set forth in item [16] of the Office action mailed January 05, 2004 is withdrawn. See also applicants' supporting argument at pages 21-22 of the instant response.

Claim Rejections - 35 USC § 103

[17] The rejection of claim(s) 66-71, 84-85, 87, and 89-91 under 35 U.S.C. 103(a) as being unpatentable over Benton et al. (US Patent 6,037,123; cited as IDS reference A1 in the IDS filed July 07, 2003) in view of Burgett et al. (US Patent 6,162,617) and Harbarth et al. (*Arch Intern Med* 158:182-189; cited as reference A20 in the IDS filed December 23, 2002) is maintained for the reasons of record as set forth in item [17] of the Office action mailed January 05, 2004 and for the reasons stated below.

In summary, Benton et al. teach a nucleic acid isolated from S. aureus encoding a polypeptide that has strong similarity to the dnaG genes of L. monocytogenes, L.

lactis, B. subtilis, and E. coli encoding DNA primases, is 100% identical to amino acids 1-50 and 561-599 of SEQ ID NO:2 and shares 93.25% similarity to SEQ ID NO:2, and teach methods for evaluating their gene as a therapeutic target. Benton et al. do not teach a polypeptide encoded by their nucleic acid. Burgett et al. teach cloning of the dnaG gene of Streptococcus pneumoniae, expressing the protein encoded by the dnaG gene for screening novel antibiotics, and disclose motivation for screening for novel antibiotics against S. pneumoniae. Harbarth et al. provide additional motivation for screening for novel antibiotics against S. pneumoniae.

Addressing claims 66-71, applicants argue the examiner disregarded the limitation of claims 66-71 requiring the claimed polypeptide to bind a bacteriophage polypeptide and thus the examiner allegedly did not include all claim limitations in the rejection and consequently did not establish a prima facie case of obviousness. Applicants argue that, while the examiner states in the rejection that such an activity of binding a bacteriophage polypeptide is an inherent characteristic of the polypeptide encoded by Benton et al., that which is inherent in the prior art cannot form the basis for an obviousness rejection under 35 USC 103(a), citing In re Shetty, 566 F2d 81, 195 USPQ 753 (CCPA 1977), In re Naylor, 369 F2d765, 768, 152 USPQ 106, 108 (CCPA 1966), and Kloster Speedsteel AB v. Crucible Inc., 793 F2d 1565, 1576, 230 USPQ 81, 88 (Fed Cir 1986). Applicants argue that the examiner was illegally incorrect in relying on inherency as a teaching or suggestion of an essential property of the claimed polypeptides. Applicants' argument has been fully considered but is not found persuasive.

Although the cited references are silent as to whether the polypeptide encoded by Benton et al. has the ability to bind to a bacteriophage polypeptide, this is immaterial as the encoded polypeptide necessarily possesses this characteristic as indicated by the evidence provided by the examiner, i.e., that the polypeptide encoded by the nucleic acid of Benton et al. has amino acids 561-599 of SEQ ID NO:2, which impart bacteriophage binding activity. MPEP 2112.01 states, "[w]here the claimed and prior art products are identical or substantially identical in structure or composition... ...a prima facie case of either anticipation or obviousness has been established and, citing In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990), states, "[w]hen the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." MPEP 2112.01 states that "the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product." (emphasis in original). In this case, the polypeptide encoded by the polynucleotide of Benton et al. is 93% identical and 96% similar to the full length of the polypeptide of SEQ ID NO:2 and is 100% identical to amino acids 1-50 and 561-599 of SEQ ID NO:2 (See Appendix B). As the polypeptide encoded by Benton et al. satisfies the structural limitations of the claimed polypeptide, according to MPEP 2112.01, a prima facie case of obviousness has been established. Moreover, as the polypeptide encoded by the nucleic acid of Benton et al. comprises amino acids 561-599 of SEQ ID NO:2, which is asserted to be required for bacteriophage polypeptide binding, the polypeptide encoded by the nucleic acid of Benton et al. has the inherent characteristic of bacteriophage

polypeptide binding, which is undisputed by applicants. In this case, applicants have failed to provide evidence to distinguish the polypeptide encoded by Benton et al. (that is obvious in view of the cited references) from the claimed polypeptide and thus, the cited references render obvious the claimed polypeptide.

Applicants argue the examiner has not presented a clear and convincing motivation for combining the references because Benton et al. teach that the nucleic acid and encoded amino acid sequences reveal identity to plaC, encoding an S. aureus DNA-directed RNA polymerase, and those wishing to express a DnaG primase would have been discouraged and not motivated to express the protein encoded by the nucleic acid of Benton et al. Applicants' argument is not found persuasive.

There is no dispute that Benton et al. disclose a relation of "one end" of their clone to an S. aureus DNA-directed RNA polymerase. Contrary to applicants' assertion, nowhere do Benton et al. suggest that "the polypeptide disclosed therein may be a RNA polymerase, not a DNA primase." It is clear from the additional teachings of Benton et al., which appear to have been ignored by applicants, that the polypeptide encoded by their nucleic acid is not an S. aureus DNA-directed RNA polymerase. As evidence thereof, Benton et al. additionally teach that their clone does not contain the entire S. aureus DNA-directed RNA polymerase ORF and explicitly state that their nucleic acid is a dnaG ORF. Thus, in view of the reference of Benton et al., taken as a whole, one of ordinary skill in the art would have no expectation that the polypeptide encoded by the nucleic acid of Benton et al. would be a S. aureus DNA-directed RNA polymerase.

Based on the teachings of Benton et al. as a whole, one would clearly recognize that the polypeptide encoded by the nucleic acid of Benton et al. is a DnaG primase.

In order to clarify the record, it is noted that applicants admit that Benton et al. disclose a polypeptide (see page 25, line 12 of the response). Applicants are advised that this statement, if maintained, may be used in a rejection under 35 USC 102(e). The examiner requests that applicants clarify this statement in the response to this Office action.

Applicants argue that a skilled artisan would not have a reasonable expectation of success for making the claimed polypeptide in view of the results of Benton et al. because: 1) Benton et al. teach that their nucleic acid has identity to an S. aureus DNA-directed RNA polymerase and only similarity to a DnaG polypeptide; 2) neither Benton et al. nor Burgett et al. identify the correct ORF of the encoded protein, and give no indication or direction as to which of the possible choices (of reading frames) is likely to be successful for expressing an S. aureus DnaG primase polypeptide; 3) the courts have found that "obvious to try" is not a legitimate test for patentability; and 4) the examiner has used hindsight reasoning to construct the instant rejection. Applicants' argument is not found persuasive.

Regarding argument 1), as stated above, applicants have ignored the teachings of Benton et al. as a whole. Benton et al. teach that their clone does not contain the entire S. aureus DNA-directed RNA polymerase ORF, state that their clone "has strong similarity at the peptide level" with DnaG primases from other microorganisms, and explicitly state that their nucleic acid is a dnaG ORF. Thus, one of ordinary skill in the art

would have no expectation that the polypeptide encoded by the nucleic acid of Benton et al. would be a S. aureus DNA-directed RNA polymerase and would instead recognize that the polypeptide encoded by the nucleic acid of Benton et al. is a DnaG primase. Addressing argument 2), applicants have failed to recognize the state of the art and the skill of one of ordinary skill in the art at the time of the invention. MPEP 2143.01, citing In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000), states, "[t]he test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art" (underline added for emphasis). Benton et al. disclose their nucleic acid encodes a polypeptide having "strong similarity at the peptide level" with DnaG primase polypeptides from other microorganisms, and provide references for the corresponding DnaG primase of L. monocytogenes and also cite other microorganisms having DnaG primases whose sequences have similarity to that of the polypeptide encoded by the nucleic acid of Benton et al. At the time of the invention, one of ordinary skill in the art would have the knowledge and skill to translate the nucleic acid of Benton et al. into a polypeptide sequence and compare this sequence with the polypeptide sequence of the DnaG primase of L. monocytogenes as cited by Benton et al. While Benton et al. do not disclose a particular degree of similarity of the polypeptide encoded by their nucleic acid to other DnaG primases, one need only to select the encoded polypeptide having the strongest similarity to the other DnaG primases. Argument 3) is without merit as the combination of references in view of the state of the art and the knowledge and skill of one of ordinary skill in the art at the time

of the invention provide an enabling disclosure, provide a clear suggestion to express the polypeptide encoded by Benton et al., and provide a reasonable expectation of success for making such polypeptide. Regarding argument 4), it is noted that it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As the teachings relied upon by the examiner are either expressly stated in the cited prior art references or are well within the level of ordinary skill at the time of the invention, the rejection is proper as written.

Conclusion

[18] Status of the claims:

- Claims 66-72 and 84-91 are pending.
- Claims 66-72, 84-87, and 89-91 are rejected.
- Claim 88 appears to be in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

05-25-04

Patent Examiner
Art Unit 1652

05-24-04

APPENDIX A

```
RESULT 2
AAY49072
ID   AAY49072 standard; Protein; 572 AA.
XX
AC   AAY49072;
XX
DT   05-JAN-2000  (first entry)
XX
DE   Amino acid sequence encoded by partial dnaG gene.
XX
KW   Gram positive bacteria; dnaE; dnaX; dnaB; PolC; dnaN; dnaG; helicase;
KW   alpha subunit; DNA polymerase III holoenzyme; gamma subunit; tau subunit;
KW   primase; clamp loader; glue protein; replication; antibiotic.
XX
OS   Staphylococcus aureus.
XX
PN   WO9937661-A1.
XX
PD   29-JUL-1999.
XX
PF   25-JAN-1999;   99WO-US01547.
XX
PR   27-JAN-1998;   98US-0074522.
PR   22-JUL-1998;   98US-0093727.
XX
PA   (UYRQ ) UNIV ROCKEFELLER.
XX
PI   O'Donnell ME,  Zhang D,  Whipple R;
XX
DR   WPI; 1999-590685/50.
DR   N-PSDB; AAZ31006.
XX
PT   New isolated dnaE, dnaX and dnaB genes from Gram positive bacteria,
PT   used to develop screening assays for identifying antibiotic compounds
PT   -
XX
PS   Disclosure; Page 33-34; 132pp; English.
XX
CC   This is the amino acid sequence encoded by the Staphylococcus aureus
CC   partial dnaG gene. The invention relates to a number of isolated DNA
CC   molecules from Gram positive bacterium, corresponding to dnaE
CC   (AAZ31001), dnaX (AAZ31002),and dnaB (AAZ31003). The PolC, dnaN and dnaG
CC   genes (AAZ31004-Z31006) are also identified. The dnaE gene corresponds to
CC   the alpha subunit of the Escherichia coli, DNA polymerase III
CC   holoenzyme, dnaX corresponds to the gamma and tau subunits, and dnaB
CC   corresponds to the helicase. The alpha subunit is the actual DNA
CC   polymerase, the gamma complex forms the clamp loader and tau is a "glue
CC   protein". DnaX encodes both gamma and Tau, Tau is the product of the full
CC   gene, while gamma is the product of the first two thirds of the gene.
CC   DnaN forms the beta subunit which forms the sliding clamp, and dnaG
CC   encodes a primase. The DNA sequences of the invention can be used to
CC   identify agents that inhibit or promote DNA replication by acting on
CC   various parts of the gram positive bacterial DNA polymerase holoenzyme.
CC   The products and methods of the invention can be used for identifying
CC   pharmacological agents or lead compounds for agents active at the level
CC   of a replication protein function, particularly DNA replication. The
CC   agents identified can be used as antibiotics.
XX
SQ   Sequence   572 AA;

  Query Match             93.5%;  Score 2906;  DB 20;  Length 572;
  Best Local Similarity   98.1%;  Pred. No. 6.4e-220;
  Matches  560;  Conservative    3;  Mismatches    2;  Indels    6;  Gaps    1;

Qy         35 IGLCPFHDEKTPSFTVSEDKQICHCFGCKKGGNVFQFTQEIKDISFVEAVKELGDRVNVA 94
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db          2 IGLCPFHDEKTPSFTVSEDKQICHCFGCKKGGNVFQFTQEIKDISFVEAVKELGDRVNVA 61

Qy         95 VDIEATQSNSNVQIASDDLQMIEMHELIQEFYYYALTKTVEGEQALTYLQERGFTDALIK 154
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         62 VDIEATQSNSNVQIASDDLQMIEMHELIQEFYYYALTKTVEGEQALTYLQERGFTDALIK 121

Qy        155 ERGIGFAPDSSHFCHDFLQKKGYDIELAYEAGLLSRNEENFSYYDRFRNRIMFPLKNAQG 214
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        122 ERGIGFAPDSSHFCHDFLQKKGYDIELAYEAGLLSRNEENFSYYDRFRNRIMFPLKNAQG 181

Qy        215 RIVGYSGRTYTGQEPKYLNSPETPIFQKRKLLYNLDKARKSIRKLDEIVLLEGFMDVIKS 274
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        182 RIVGYSGRTYTGQEPKYLNSPETPIFQKRKLLYNLDKARKSIRKLDEIVLLEGFMDVIKS 241

Qy        275 DTAGLKNVVATMGTQLSDEHITFIRKLTSNITLMFDGDFAGSEATLKTGQNLLQQGLNVF 334
              ||||||||||||||||||||||||||||||||||||||||||||||||:|||||||||
Db        242 DTAGLKNVVATMGTQLSDEHITFIRKLTSNITLMFDGDFAGSEATLKTGQHLLQQGLNVF 301

Qy        335 VIQLPSGMDPDEYIGKYGNDAFTAFVKNDKKSFAHYKVSILKDEIAHNDLSYERYLKELS 394
              |||||||||||||||||||| ||||||||||||||||||||||||||||||||||||||
Db        302 VIQLPSGMDPDEYIGKYGNDAFTTFVKNDKKSFAHYKVSILKDEIAHNDLSYERYLKELS 361

Qy        395 HDISLMKSSILQQKALNDVAPFFNVSPEQLANEIQFNQAPANYYPE------DEYGGYIE 448
              ||||||||||||||:|||||||||||||||||||||||||||||||      ||||||||
Db        362 HDISLMKSSILQQKAINDVAPFFNVSPEQLANEIQFNQAPANYYPEDEYGGYDEYGGYIE 421

Qy        449 PEPIGMAQFDNLSRQEKAERAFLKHLMRDKDTFLNYYESVDKDNFTNQHFKYVFEVLHDF 508
              ||||||||||||||:||||||||||||||||||||||||||||||||||||||||||||
Db        422 PEPIGMAQFDNLSRREKAERAFLKHLMRDKDTFLNYYESVDKDNFTNQHFKYVFEVLHDF 481

Qy        509 YAENDQYNISDAVQYVNSNELRETLISLEQYNLNDEPYENEIDDYVNVINEKGQETIESL 568
              |||||||||||||||||||||||||||||||| ||||||||||||||||||||||||||
Db        482 YAENDQYNISDAVQYVNSNELRETLISLEQYNLNGEPYENEIDDYVNVINEKGQETIESL 541

Qy        569 NHKLREATRIGDVELQKYYLQQIVAKNKERM 599
              |||||||||||||||||||||||||||||||
Db        542 NHKLREATRIGDVELQKYYLQQIVAKNKERM 572
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APPENDIX B

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RESULT 7
AR149331
LOCUS       AR149331               2687 bp    DNA     linear   PAT 08-AUG-2001
DEFINITION  Sequence 34 from patent US 6228588.
ACCESSION   AR149331
VERSION     AR149331.1  GI:15113922
KEYWORDS    .
SOURCE      Unknown.
  ORGANISM  Unknown.
            Unclassified.
REFERENCE   1  (bases 1 to 2687)
  AUTHORS   Benton,B., Lee,V.J., Malouin,F., Martin,P.K., Schmid,M.B. and
            Sun,D.
  TITLE     Methods of screening for compounds active on Staphylococcus aureus
            target genes
  JOURNAL   Patent: US 6228588-A 34 08-MAY-2001;
FEATURES             Location/Qualifiers
     source          1. .2687
                     /organism="unknown"
BASE COUNT     1026 a    342 c    479 g    812 t     28 others
ORIGIN

Alignment Scores:
Pred. No.:              1.43e-184      Length:         2687
Score:                  2899.00        Matches:        580
Percent Similarity:     95.72%         Conservative:   1
Best Local Similarity:  95.55%         Mismatches:     18
Query Match:            93.25%         Indels:         8
DB:                     6              Gaps:           0

US-10-025-222A-2 (1-599) x AR149331 (1-2687)

Qy          1 LeuArgIleAspGlnSerIleIleAsnGluIleLysAspLysThrAspIleLeuAspLeu 20
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        484 TTGCGAATAGATCAATCGATCATTAATGAAATAAAAGATAAAACCGACATTTTAGACTTG 543

Qy         21 ValSerGluTyrValLysLeuGluLysArgGlyArgAsnTyrIleGlyLeuCysProPhe 40
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        544 GTAAGTGAATATGTWAAATTAGAAAAGAGAGGACGCAATTATATAGGTTTGTGTCCTTTT 603

Qy         41 HisAspGluLysThrProSerPheThrValSerGluAspLysGlnIleCysHisCysPhe 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        604 CATGATGAAAAGACACCTTCATTTACAGTTTCTGAAGATAAACAAATTTGTCATTGTTTT 663

Qy         61 GlyCysLysLysGlyGlyAsnValPheGlnPheThrGlnGluIleLysAspIle-SerPh 80
              |||||||||||||||||||||||||||||||||||||||||||||||||||| |||||
Db        664 GGTTGTAAAAAAGGTGGCAATGTTTTCCAATTTACTCAAGAAATTAAAGACATATTCATT 723

Qy         80 eValGluAlaValLysGluLeuGly-AspArgValAsnVal-AlaValAspIleGluAla 99
              ||||  ||||||||||||||||||  ||||||||||| ||||||  |||||||||
Db        724 TGTTGAMGCGGTTAAAGAATTAGGTGGWTAGRGTTAATGTTTGCTGTAGRTATTGAGGCA 783

Qy        100 ThrGlnSer-AsnSerAsnValGlnIleAlaSerAspAspLeuGlnMetIleGlu-MetH 119
                 ||||||    ||||||||||||||   |||      ||||||||||:::    |
Db        784 MCACAATCTTWACTCAAATGTYCAAATTSCTTCTSRYGRTTTACAAATGATTGACAWTGC 843

Qy        119 is-GluLeuIleGlnGluPheTyrTyrTyrAlaLeuThrLysThrValGluGlyGluGln 138
              ||    |||   |||   ||||||||||||||||||||||||||||||||||||||||||
Db        844 ATGGRGTTAWTACAAGRATTTTATTATTACGCTTTAACAAAGACAGTCGAAGGCGAACAA 903

Qy        139 AlaLeuThrTyrLeuGlnGluArgGlyPheThrAspAlaLeuIleLysGluArgGlyIle 158
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        904 GCATTAACGTACTTACAAGAACGTGGTTTTACAGATGCGCTTATTAAAGAGCGAGGCATT 963

Qy        159 GlyPheAlaProAspSerSerHisPheCysHisAspPheLeuGlnLysLysGlyTyrAsp 178
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db        964 GGCTTTGCACCCGATAGCTCACATTTTTGTCATGATTTTCTTCAAAAAAAGGGTTACGAT 1023

Qy        179 IleGluLeuAlaTyrGluAlaGlyLeuLeuSerArgAsnGluGluAsnPheSerTyr-Ty 198
              |||||||||||||||||||||||||||   |||||||||||||||||||||||||| ||
Db       1024 ATTGAATTAGCATATGAAGCCGGATTATWATCACGTAACGAAGAAAATTTCAGTTATTTA 1083

Qy        198 rAspArgPheArgAsnArgIleMetPheProLeuLysAsnAlaGlnGlyArgIleValGl 218
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1084 CGATAGATTYCGAAAYCGTATTATGTTYCCTTTGAAAAATGCGCAAGGAAGAATTGTTGG 1143

Qy        218 yTyrSerGlyArgThrTyrThrGlyGlnGluProLysTyrLeuAsnSerProGluThrPr 238
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1144 ATATTCAGGTCGAACATATACCGGTCAAGAACCAAAATACTTAAATAGTCCTGAAACACC 1203

Qy        238 oIlePheGlnLysArgLysLeuLeuTyrAsnLeuAspLysAlaArgLysSerIleArgLy 258
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1204 TATCTTTCAAAAAAGAAAGTTGTTATACAACTTAGATAAAGCGCGTAAATCAATTAGAAA 1263

Qy        258 sLeuAspGluIleValLeuLeuGluGlyPheMetAspValIleLysSerAspThrAlaGl 278
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1264 ATTAGATGAAATCGTATTACTAGAAGGTTTTATGGATGTTATAAAATCTGATACTGCTGG 1323

Qy        278 yLeuLysAsnValValAlaThrMetGlyThrGlnLeuSerAspGluHisIleThrPheIl 298
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1324 CTTGAAAAACGTTGTTGCAACAATGGGTACACAGTTGTCAGATGAACATATTACTTTTAT 1383

Qy        298 eArgLysLeuThrSerAsnIleThrLeuMetPheAspGlyAspPheAlaGlySerGluAl 318
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1384 ACGAAAGTTAACATCAAATATAACATTAATGTTTGATGGGGATTTTGCGGGTAGTGAAGC 1443

Qy        318 aThrLeuLysThrGly-GlnAsnLeuLeuGlnGlnGlyLeuAsnValPheValIleGlnL 338
              |||||||||||||||| |||||||||||||||||||||||||||||||   |||||||
Db       1444 AACACTTAAAACAGGTYCAAAATTTGTTACAGCAAGGGCTAAATGTRTTTKTTATACAAT 1503

Qy        338 euProSerGlyMetAspProAspGluTyrIleGlyLysTyrGlyAsnAspAlaPheThrA 358
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||   |
Db       1504 TGCCATCAGGCATGGATCCGGATGAATACATTGGTAAGTATGGCAACGATGCATTTMCTG 1563

Qy        358 laPheValLysAsnAspLysLysSerPheAlaHisTyrLysValSerIleLeuLysAspG 378
              |||||   ||||||||||||||||||||   ||||||||||||||||||||||||||||||
Db       1564 CTTTTSTAAAAAATGACAAAAAGTCATTTSCACATTATAAAGTGAGTATATTAAAAGATG 1623

Qy        378 luIleAlaHisAsnAspLeuSerTyrGluArgTyrLeuLysGluLeuSerHisAspIleS 398
              ||||||||||||||||||||||||||||||||||||||   ||||||||||||||||
Db       1624 AAATTGCACATAATGACCTTTCATATGAACGTTATTTGAAAGAMCTAAGTCATGATATTT 1683

Qy        398 erLeuMetLysSerSerIleLeuGlnGlnLysAlaLeuAsnAspValAlaProPhePheA 418
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1684 CGCTTATGAAATCATCGATTTTGCAACAAAAGGCTTTAAATGATGTTGCACCATTTTTCA 1743

Qy        418 snValSerProGluGlnLeuAlaAsnGluIleGlnPheAsnGlnAlaProAlaAsnTyrT 438
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1744 ATGTTAGTCCTGAGCAATTAGCTAACGAAATACAATTCAATCAAGCACCAGCCAATTATT 1803

Qy        438 yrProGluAspGluTyrGlyGlyTyrIleGluProGluProIleGlyMetAlaGlnPheA 458
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1804 ATCCAGAAGATGAGTATGGCGGTTACATTGAACCTGAGCCAATTGGTATGGCACAATTTG 1863

Qy        458 spAsnLeuSerArgGlnGluLysAlaGluArgAlaPheLeuLysHisLeuMetArgAspL 478
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1864 ACAATTTGAGCCGTCAAGAAAAAGCGGAGCGAGCATTTTTAAAACATTTAATGAGAGATA 1923

Qy        478 ysAspThrPheLeuAsnTyrTyrGluSerValAspLysAspAsnPheThrAsnGlnHisP 498
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1924 AAGATACATTTTTAAATTATTATGAAAGTGTTGATAAGGATAACTTCACAAATCAGCATT 1983

Qy        498 heLysTyrValPheGluValLeuHisAspPheTyrAlaGluAsnAspGlnTyrAsnIleS 518
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                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1984 TTAAATATGTATTCGAAGTCTTACATGATTTTTATGCGGAAAATGATCAATATAATATCA 2043

Qy        518 erAspAlaValGlnTyrValAsnSerAsnGluLeuArgGluThrLeuIleSerLeuGluG 538
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2044 GTGATGCTGTGCAGTATGTTAATTCAAATGAGTTGAGAGAAACACTAATTAGCTTAGAAC 2103

Qy        538 lnTyrAsnLeuAsnAspGluProTyrGluAsnGluIleAspAspTyrValAsnValIleA 558
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2104 AATATAATTTGAATGACGAACCATATGAAAATGAAATTGATGATTATGTCAATGTTATTA 2163

Qy        558 snGluLysGlyGlnGluThrIleGluSerLeuAsnHisLysLeuArgGluAlaThrArgI 578
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2164 ATGAAAAAGGACAAGAAACAATTGAGTCATTGAATCATAAATTAAGGGAAGCTACAAGGA 2223

Qy        578 leGlyAspValGluLeuGlnLysTyrTyrLeuGlnGlnIleValAlaLysAsnLysGluA 598
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2224 TTGGCGATGTAGAATTACAAAAATACTATTTACAGCAAATTGTTGCTAAGAATAAAGAAC 2283

Qy        598 rgMet 599
                |||||
Db       2284 GCATG 2288
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